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(54) Title of the Invention: A Tablet Containing Coated Granules

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## SPECIFICATION

1. Title of the Invention

A Tablet Containing Coated Granules

2. Claims

1. A tablet containing coated granules characterized in that it is a tablet that is obtained by compression molding of medicinal drug compositions containing coated granules and in that the coated granules are further coated by a protective film of water-soluble polymer or of acid-soluble polymer.

2. A tablet as described in Claim 1 in which the film of the coated particles is comprised of one or two or more of enteric polymer or wax.

3. A tablet as described in Claim 1 or 2 in which an active medicinal drug product is contained in the coated granules.

4. A tablet as described in any one of Claims 1, 2 or 3 in which an active medicinal drug component is contained in the coated granule and non-coated granule component.

3. Detailed Description of the Invention

(Field of Industrial Use)

This invention relates to a tablet that is compression molded after the coated granules are doubly coated by a water-soluble polymer or an acid-soluble polymer. In further detail, it relates to a tablet that contains double-coated granules that prevent breakage of the film of the coated granules when a medicinal drug composition that contains coated granules is subjected to compression molding.

(Prior Art and Problems Thereof)

It is a widely used practice to apply enteric, acid soluble or insoluble films to granules to hide taste or odor and to add various functions such as sustained release. These coated granules can be supplied in unaltered form or they can be filled into hard gelatin capsules or soft gelatin capsules. When tablets are made by compression molding, the film is frequently broken by the compressive force at that time and its functions are lost or changed. For this reason, when a sustained release agent in the form of a tablet is prepared, in advance anticipation of breakage of the film by compression, a tablet is made from which release is further controlled by coating with an insoluble polymer, after which compression molding is performed and the tablet is made. However, breakage of the film at the time of compression molding is controlled by the state of the film and the properties of the uncoated portion so that its prediction is extremely difficult. For this reason, the release characteristics of the tablets that are obtained frequently differ from what was predicted in advance.

(Means for Solving the Problems)

Under these circumstances, the inventors conducted intensive research on breakage of films when coated films were subjected to compression molding. As a result, they perfected this invention by discovering that breakage of films can be prevented without loss of the characteristics and functions of the coated granules when tablets are obtained by coating the coated granules with a water-soluble polymer or an acid-soluble polymer and they are then subjected to compression molding.

Specifically, this invention provides a tablet that contains coated granules characterized in that it is a tablet that is obtained by compression molding of medicinal drug compositions containing coated granules and in that the coated granules are further coated by a protective film of water-soluble polymer or of acid-soluble polymer.

The water-soluble polymer or acid-soluble polymer that is used in this invention has the role of protecting the coated granules so that the functions of the film of the coated granules essentially do not change when it is administered to an individual and so that they are resistant to compressive force when compression is applied. Consequently, there are no particular limitations on the protective film that is used in this invention as long as it is a water-soluble polymer or an acid-soluble polymer that can play the aforementioned role. Desirable specific examples of water-soluble polymers include hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, polyvinyl pyrrolidone, polyethylene glycol and gelatin and desirable examples of acid-soluble polymers include aminoalkyl methacrylate copolymer E and polyvinyl acetal diethylaminoacetate. These polymers may be used individually or they may be used in mixtures of two or more. If the coated granules can be protected so that there is essentially no impairment of the functions of the films of the coated granules when they are administered in the body and so that they are resistant to compressive force when compressive force is applied, they may be used mixed with enteric or insoluble polymers or with waxes.

HPMC a PEG

There are no particular limitations on the amount of coating of water-soluble polymer or acid-soluble polymer that is used in this invention, the amount being determined in conjunction with the properties of the coated granules and with the properties of the vehicle with which the tablet is made. Ordinarily, it is in the range of 5 to 50%.

In preparing the tablet preparation of this invention, first, the coated granules are coated by standard methods with a water-soluble polymer or an acid soluble polymer and two types of coated granules are prepared. At this time, as required, suitable plasticizers, lubricants and colorants can be added. Next, the two types of coated granules, as required, can be mixed with conventional, known compositions for tablet making, including suitable vehicles, binders, disintegrating agents, lubricants, colorants, fragrances and stabilizers and the tablets can be manufactured by compression molding.

Further, the films of the coated granules are sustained release or enteric films and active medicinal drug products can be compounded with the protective film part or the uncoated granule part in order to obtain blood concentrations of a certain degree after administration.

Further, the tablets of this invention can be made as nucleated tablets, multilayer tablets, film coated tablets and sugar-coated tablets by means of methods that are ordinarily used.

(Action and Effect)

As a result of the action of water-soluble polymer coatings or acid soluble polymer coatings, the tablets containing coated granules of this invention obtained in this way do not undergo loss of the function of the films of the coated particles and the desired effect can be obtained even when compression molding treatment is performed.

(Examples)

We shall now describe this invention in detail by presenting examples of this invention.

Example 1

Manufacture of bare granules a:

800 g of Diclofenac sodium and 400 g of corn starch were mixed and finely pulverized, with a fine powder being obtained. Using 600 g of white sugar that had been adjusted to 28 ~ 35 mesh, the fine powder was subjected to tumble granulation. A solution consisting of 25 g of hydroxypropyl cellulose dissolved in 475 g of ethyl alcohol was poured on it, with spherical granules being manufactured. They were then dried for 3 hours at 55°C. Dry granules that could pass through 16 mesh but that could not pass through 35 mesh were selected as bare granules a.

Example 2

Manufacture of coated granules b:

800 g of the bare granules a manufactured in Example 1 were introduced into a fluidized bed coating device, spray coating was performed by a standard method with 2746 g of a coating solution of the composition indicated below, with the coated granules b being manufactured. The amount of coating was 23% relative to the bare granules.

| Composition | % |
|---|---|
| Methacrylic acid polymer L | 6.5 |
| Talc | 0.2 |
| Ethyl alcohol | 93.3 |
| Total | 100.0 |

Example 3

Manufacture of double coated granules c

500 g of the coated granules b manufactured in Example 2 were introduced into a fluidized bed coating device and spray coating was performed by a standard method with 1389 g of a coating solution of the composition indicated below, with the double coated granules c being manufactured. The amount of coating was 20% relative to the bare granules b.

| Composition | % |
|---|---|
| Hydroxypropyl methyl cellulose | 6.5 |
| Macrogol 6000 | 0.5 |
| Talc | 0.2 |
| Ethyl alcohol | 66.8 |
| Purified water | 27.0 |
| Total | 100.0 [sic] |

Example 4

Manufacture of tablet of this invention

125 g of 50% ethyl alcohol solution of 10 % (w/w) hydroxypropyl cellulose was added to and kneaded with a mixture of 240 g of crystalline cellulose, 25 g of corn starch and 172.5 g of lactose and granules were manufactured by a standard method. Next, 203.6 g of these granules, 188.4 g of the double coated granules c obtained in Example 3, 20 g of carboxymethylcellulose calcium, 4 g of magnesium stearate and 4 g of talc were mixed uniformly, after which the mixture was compression molded and tablets of this invention of a weight of 400 mg and a diameter of 10 mm per tablet were manufactured.

Example 5

Manufacture of Comparison Tablet

125 g of 50% ethyl alcohol solution of 10 % (w/w) hydroxypropyl cellulose was added to and kneaded with a mixture of 240 g of crystalline cellulose, 25 g of corn starch and 172.5 g of lactose and granules were manufactured by a standard method. Next, 203.6 g of these granules, 140.3 g of the coated granules b obtained in Example 2, 20 g of carboxymethylcellulose calcium, 4 g of magnesium stearate and 4 g of talc were mixed uniformly, after which the mixture was compression molded and tablets of this invention of a weight of 400 mg and a diameter of 10 mm per tablet were manufactured.

Example 6

Determinations were made at 100 r.p.m. by the rotating paddle method (Japanese Pharmacopoeia, 11th Revised Edition) using as eluates solutions of the tablets of this invention obtained in Example 4, the comparison tablets obtained in Example 5 and the coated granules b using a test solution of pH 4.5 up to 30 minutes from the beginning of the reaction and a test solution (Japanese Pharmacopoeia, 11th Revised Edition, Solution 2) from 30 minutes to 60 minutes. The results are shown in Table 1. The tablets of this invention did not undergo breaking of the film as did the comparison tablets and exhibited the same elution characteristics as the comparison tablets.

Table 1

| Elapsed time (minutes) | Elution rate (%) | | |
|---|---|---|---|
| | Example 4 (This invention) | Example 5 (Comparison example) | Coated granules b (Comparison example) |
| pH 4.5<br>30 | 1.5 | 21.5 | 1.2 |
| pH 6.8<br>60 | 99.7 | 98.5 | 99.2 |

Example 7

Manufacture of bare granules d

The bare granules d were obtained in the same way as in Example 1 using a solution comprised of 800 g of theophylline, 375 g of cornstarch, 600 g of white sugar of a granule size adjusted to 28 ~ 35 mesh and 25 g of hydroxypropyl cellulose dissolved in 475 g of ethyl alcohol.

Example 8

Manufacture of coated granules e:

800 g of the bare granules d manufactured in Example 7 were introduced into a fluidized bed coating device and spray coating was performed by a standard method with 1684 g of coating solution of the composition indicated below, with coated granules e being manufactured. The amount of coating was 8% relative to the coated granules e.

| Composition | % |
|---|---|
| Ethyl cellulose | 2.7 |
| Polyvinyl pyrrolidone K30 | 0.9 |
| Talc | 0.2 |
| Ethyl alcohol | 96.2 |
| Total | 100.0 |

Example 9

Manufacture of double coated granules f used in this invention:

600 g of the coated granules e manufactured in Example 8 were introduced into a fluidized bed coating device and spray coating was performed by a standard method with 2000 g of a coating solution of the composition indicated below, with the double coated granules f being manufactured. The amount of coating was 20% relative to the coated granules e.

| Composition | % |
|---|---|
| Polyvinyl acetal diethylaminoacetate | 6.0 |
| Ethyl alcohol | 47.0 |
| Acetone | 47.0 |
| Total | 100.0 |

Example 10

Manufacture of tablets of this invention

147.8 g of double coated granules f, 150 g of crystalline cellulose, 46.2 g of lactose, 3 g of magnesium stearate and 3 g of talc were mixed uniformly, after which the mixture was subjected to compression molding, with tablets of this invention of a weight of 350 mg and a diameter of 9 mm per tablet being manufactured.

Example 11

Manufacture of comparison tablets:

123.2 g of coated granules e, 150 g of crystalline cellulose, 70.8 g of lactose, 3 g of magnesium stearate and 3 g of talc were mixed uniformly and the mixture was subjected to compression molding, with tablets of a weight of 350 mg and a diameter of 9 mm per tablet being manufactured.

Example 12

Determinations were made at 100 r.p.m. by the rotating paddle method (Japanese Pharmacopoeia, 11th Revised Edition) of solutions of the tablets of this invention obtained in Example 10, the comparison tablets obtained in Example 11 and the coated granules e using a solution of pH 1.2 as the eluate. The results are shown in Table 2. The tablets of this invention exhibited essentially the same elution characteristics as the comparison tablets and there were no changes in the elution rate as occurred with the comparison tablets.

Table 2

| Elapsed time (minutes) | Elution rate (%) | | |
|---|---|---|---|
| | Example 10 (This invention) | Example 11 (Comparison example) | Coated granules e (Comparison example) |
| 1 | 25.0 | 45.3 | 24.5 |
| 5 | 56.5 | 81.2 | 54.2 |

Example 13

Manufacture of bare granules g

A solution consisting of 40 g of hydroxypropyl cellulose dissolved in 760 g of ethyl alcohol was added to and kneaded with a mixture of 1400 g of Cephalexin, 160 g lactose, 200 g of purified white sugar and 200 g of crystalline cellulose. This mixture was granulated using a cylindrical granulating machine, after which spherical tablets were manufactured using a rounding machine. They were then dried for 2 hours at 55°C. Of these dried granules, those that passed through 16 mesh but that did not pass through 35 mesh were designated as bare granules g.

Example 14

Manufacturer of coated granules h:

800 g of the coated granules g manufactured in Example 13 were introduced into a fluidized bed coating device and spray coating was performed by a standard method with 3582 g of coating solution of the composition of Example 2, with the coated granules h being manufactured. The amount of coating was 30% relative to the coated granules g.

Example 15

Manufacture of double coated granules i

400 g of the coated granules h manufactured in Example 14 were introduced into a fluidized bed coating device and spray coating was performed by a standard method with 1111 g of coating solution of the composition of Example 3, with the double coated granules i being manufactured. The amount of coating was 20% relative to the coated granules h.

Example 16

Manufacture of tablets of this invention:

A solution consisting of 10 g of hydroxypropyl cellulose dissolved in 190 g of ethyl alcohol was added to and kneaded with a mixture of 700 g of Cephalexin, 90 g of lactose and 200 g of purified white sugar, the mixture was dried for 2 hours at 55°C and granules were manufactured by a standard method. Next, 53.6 g of these granules, 195 g of the double coated granules i of Example 15, 143.4 g of crystalline cellulose, 4 g of magnesium stearate and 4 g of talc were mixed uniformly, after which the mixture was subjected to compression molding, with tablets of this invention of a weight of 800 mg and a diameter of 13 mm per tablet being manufactured.

Example 17

Manufacture of comparison tablets:

A solution consisting of 10 g of hydroxypropyl cellulose dissolved in 190 g of ethyl alcohol was added to and kneaded with a mixture of 700 g of Cephalexin, 90 g of lactose and 200 g of purified white sugar, the mixture was dried for 2 hours at 55°C and granules were manufactured by a standard method. Next, 53.6 g of these granules, 162.5 g of the coated granules h of Example 14, 143.4 g of crystalline cellulose, 32.5 g of lactose, 4 g of magnesium stearate and 4 g of talc were mixed uniformly, after which the mixture was subjected to compression molding, with tablets of this invention of a weight of 800 mg and a diameter of 13 mm per tablet being manufactured.

Example 18

Manufacture of comparison granule preparation:

10.7 g of the bare granules g and 32.5 g of coated granules h were mixed, after which they were separated into packets of 432 mg and granule preparations were made.

Example 19

Determinations were made at 100 r.p.m. by the rotating paddle method (Japanese Pharmacopoeia, 11th Revised Edition) using as eluates solutions of the tablets of this invention obtained in Example 16, the comparison tablets obtained in Example 17 and the coated granules of Example 18 using a test solution (Japanese Pharmacopoeia, 11th Revised Edition, Solution 1) of pH 1.2 up to 30 minutes from the beginning of the reaction and a test solution (Japanese Pharmacopoeia, 11th Revised Edition, Solution 2) of pH 6.8 from 30 minutes to 60 minutes. The results are shown in Table 3. The elution characteristics of the tablets of this invention did not undergo any particular changes by comparison to the comparison tablets, whereas, by contrast, there were very great changes in elution characteristics in the comparison tablets.

Table 3

| Elapsed time (minutes) | Elution rate (%) | | |
|---|---|---|---|
| | Example 16 (This invention) | Example 17 (Comparison example) | Example 18 (Comparison example) |
| pH 1.2<br>30 | 33.5 | 52.1 | 30.9 |
| pH 6.8<br>60 | 98.7 | 98.5 | 98.1 |

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ABSTRACT:

PURPOSE:To obtain the subject tablet resistant to the collapse of the coating film of coated granule in compression-molding by coating a coated granule further with a protecting coating film of a water-soluble or acid soluble polymer.

CONSTITUTION:A coated granule, e.g., granule coated with an insoluble polymer, an enteric polymer or wax is coated with a protecting coating film of a water- soluble polymer (e.g., hydroxypropyl methylcellulose, polyvinyl pyrrolidone or gelatin) or an acid-soluble polymer (e.g., polyvinyl acetal diethylaminoacetate) and is compression-molded to obtain the objective tablet. The breakage of the coating film in the compression molding can be avoided and a tablet keeping expected releasing characteristic can be prepared.